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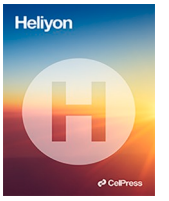

Research article

# Left ventricular ejection fraction <60 % is associated with short-term functional disability in patients of acute ischemic stroke

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ABSTRACT

*Background and objective:* The association between cardiac dysfunction and functional outcome in acute ischemic stroke (AIS) is not clear. We aimed to investigate the relationship between the routinely assessed left ventricular ejection fraction (LVEF) and functional outcomes in patients with AIS.

*Methods:* Data came from a prospective, observational, single-center study (Effect of Cardiac Function on Short-term Functional Prognosis in Patients with Acute Ischemic Stroke, SPARK). The LVEF was assessed with transthoracic echocardiography within 7 days of stroke onset. The primary outcome was functional disability, defined as a modified Rankin Scale score of 3–6 at 90 days (range: 0–6, with higher scores indicating greater disability). We also investigated the association of the LVEF with mortality, early neurological deterioration, hospital stay, and costs. Multivariate logistic regression analysis and 2:1 propensity score matching (PSM) were performed to compare the differences in outcomes.

*Results:* A total of 1181 patients were included in this analysis, of which 87 (7.4 %) patients were found to have LVEF of <60 %. In the entire study population, LVEF<60 % was significantly associated with functional disability at 90 days (odds ratio [OR]: 1.85, 95 % confidence intervals (CI): 1.01–3.40) after adjusting for all confounders. After PSM, the association was consistently significant (OR: 5.32, 95 % CI: 3.04–9.30). However, associations of the LVEF with mortality, early neurological deterioration, hospital stay, and costs were not consistently significant across all analyses. In the subgroup analysis, the association of LVEF of <60 % with functional disability was statistically significant in patients with non-cardioembolic stroke, but not in patients with cardioembolic stroke (P for interaction = 0.872).

*Conclusions:* An LVEF of <60 % will likely increase the risk of functional disability in patients with AIS. Future strategies to prevent cardiac dysfunction in the acute phase are needed.

**Trial registration:** https://www.chictr.org.cn/, ChiCTR2300067696.

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## 1. Introduction

Many patients with stroke have cardiac disease. The Third China National Stroke Registry (CNSR-III) reported that patients with coronary heart disease and atrial fibrillation accounted for 17.3 % of patients with ischemic stroke [1]. Evidence from prospective studies indicates that a history of atrial fibrillation or cardiac failure increases the risk of poor functional outcomes after ischemic stroke [2–4]. Many patients with cardiac disease have poor cardiac pump function, which directly results in arterial and venous hemodynamic disturbances. However, few studies have investigated the relationship between cardiac function and functional outcomes.

The left ventricular ejection fraction (LVEF) is routinely assessed as a parameter to evaluate left ventricular systolic function in the management of patients with stroke. Most patients with a low LVEF have a history of cardiac disease, especially cardiac failure. Some patients have a reversible low LVEF because of brain–heart syndrome, such as Takotsubo syndrome [5]. Studies have reported that 9.6%–28.0 % of patients with acute ischemic stroke (AIS) have an impaired LVEF in the acute phase [6]. Whether it occurs before or after the stroke [7], the reduced LVEF can affect the cerebral perfusion of the ischemic core and penumbra [8,9].

It is hypothesized that lower cardiac output assessed using the LVEF may be associated with an unfavorable functional outcome after AIS. However, previous studies have not standardized the time of LVEF assessment in the acute phase. One study assessed the LVEF within 6 months of the AIS episode [10]. In this study, we tested this hypothesis and standardized the time of LVEF assessment to 7 days.

## 2. Materials and methods

### 2.1. Study design and participants

The SPARK (effect of cardiac function on short-term functional prognosis in patients with acute ischemic stroke) study is a prospective, observational, single-center study with the primary objective to determine whether cardiac function affects the functional prognosis of patients with AIS. The study was registered on the Chinese Clinical Trial Registry (https://www.chictr.org.cn/; registration number: ChiCTR2300067696) and was conducted at Tianjin Huanhu Hospital, which is the largest national stroke center in northeast China.

A total of 1357 patients with AIS were enrolled from January 19 to March 20, 2023, and followed up for functional outcomes after 90 days. The inclusion criteria were as follows: (1) age $\geq$18 years, (2) diagnosis of AIS based on neurological impairment and infarction lesions on magnetic resonance imaging, (3) time from stroke onset to admission is $\leq$ 7 days, and (4) time from stroke onset to echocardiography is $\leq$ 7 days. Patients with transient ischemic attack were not included in the study.

### 2.2. Data collection

The investigators collected data using a standardized questionnaire. Patients' demographic characteristics, medical histories, pre-stroke modified Rankin Scale (mRS) score, smoking and drinking habits, and time of stroke onset were collected based on reporting by patients or their relatives and recorded at admission. In addition, patients' blood pressure and heart rate were measured by nurses and recorded by the investigators at admission. The National Institutes of Health Stroke Scale (NIHSS) score and electrocardiographic findings were evaluated by neurologists and recorded on the first day after admission. Fasting blood tests were performed on the second day after admission. At discharge, the investigators extracted the patients' following information from the electronic medical record system: auxiliary examinations, hospital treatments, neurological deterioration after admission, stroke complications, and hospital costs. The stroke subtype based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification was evaluated by two well-trained neurologists and determined by consensus. Patient follow-up was conducted over the telephone at 90 days post-discharge. The mRS score, stroke recurrence, and death were recorded.

### 2.3. Echocardiography

Transthoracic echocardiography (TTE) using Vivid E95 (GE Healthcare, Horten, Norway) was performed by certified physicians at the ultrasonic department of Tianjin Huanhu Hospital. All patients were examined with standard M-mode, 2D color Doppler imaging. Data on the cardiac structure and atrial and ventricular functions were recorded by investigators. The LVEF was measured using biplane Simpson's rule, following the recommendations of international guidelines [11].

### 2.4. Outcome parameters

The primary outcome was functional disability, defined as an mRS score of 3–6 at 90 days (range: 0–6, with higher scores indicating greater disability). Secondary outcomes included (1) an mRS score of 2–6 at 90 days; (2) an mRS score of 3–6 at discharge; (3) an mRS score of 2–6 at discharge; (4) early neurological deterioration, defined as any increase in the NIHSS score of $\geq$2 points within 24 h after admission [12]; and (5) all-cause mortality within 90 days. In addition, we explored the associations between the LVEF and hospital stay and costs.

### 2.5. Statistical analysis

To group patients, the threshold value of the LVEF was set at 60 % (LVEF ≥60 % and LVEF <60 % groups) because 60 % is reported as a meaningful threshold to predict poor outcomes either in patients with stroke [13] or in heterogeneous populations [14]. The baseline characteristics were compared between the LVEF of ≥60 % and LVEF of <60 % groups. We used $\chi 2$ tests for categorical variables and Student's *t*-test or the Mann–Whitney *U* test for continuous variables. Furthermore, we performed 2:1 propensity score matching (PSM) with a caliper distance of 0.2 to balance the difference in confounders and population distribution between the two groups. We conducted univariate logistic regression analysis to compare the risk of different poor outcomes in the PSM groups, and multivariate logistic regression analysis in the entire population. We conducted a subgroup analysis in patients with cardioembolic stroke and patients with non-cardioembolic stroke (e.g., large-artery atherosclerosis stroke, small-artery occlusion stroke, stroke of other etiology, and undetermined stroke). Previous studies have shown that patients with AIS accompanied by cardiac disease (e.g., atrial fibrillation, coronary artery disease, heart failure, valve disorder, rheumatic heart disease, and congenital heart disease) are more likely to have poor functional outcomes [15]. We attempted to demonstrate the association between the LVEF and functional

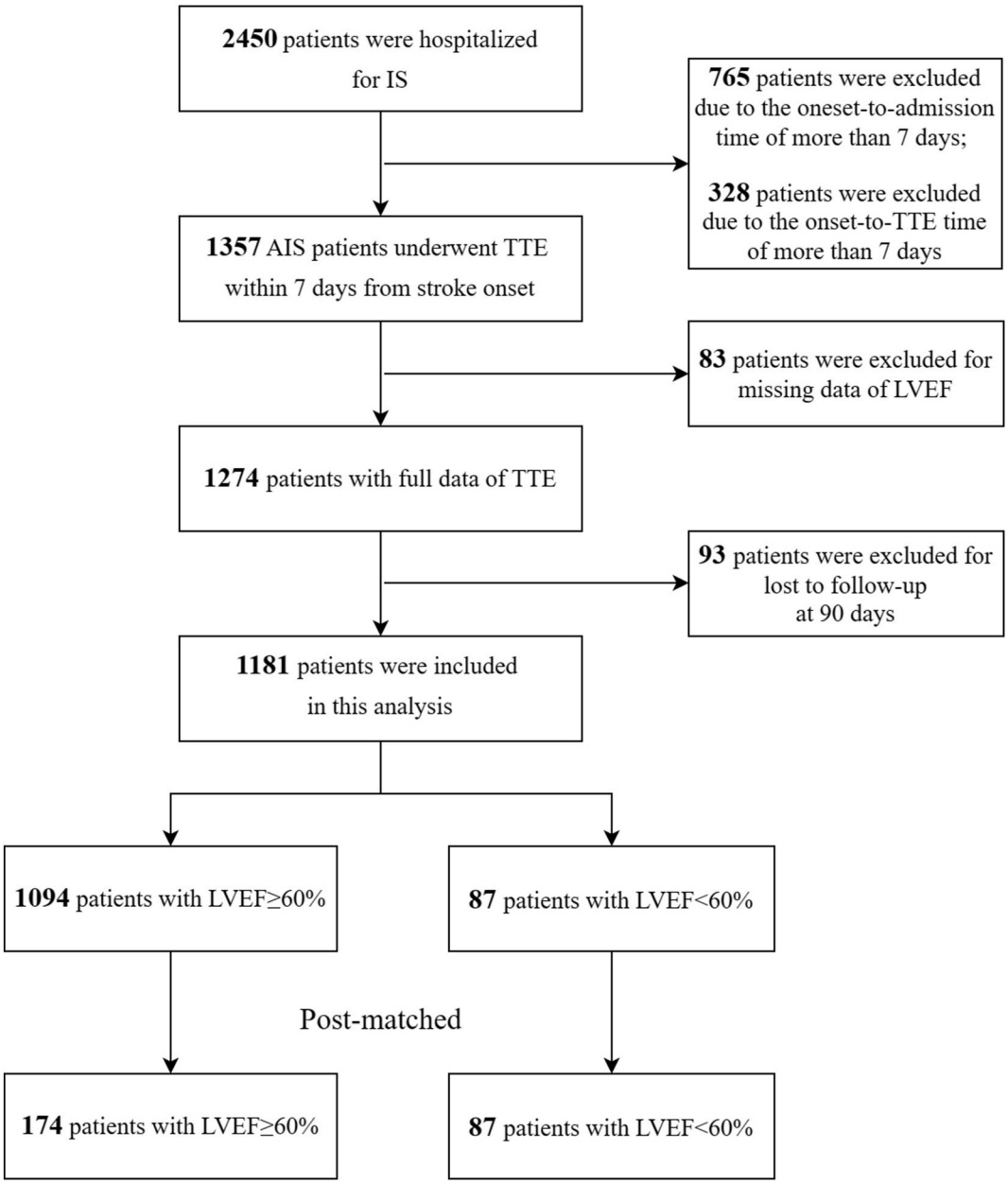


**Fig. 1.** Flowchart of patient inclusion. TTE: transthoracic echocardiography; LVEF: Left Ventricular Ejection Fraction.

outcomes in patients with AIS but without cardioembolism. In addition, we investigated the association of poor functional outcomes with the LVEF tested as a continuous variable, the LVEF grouped by 55 %, and the LVEF grouped by 50 %; the results were presented as the odds ratio (OR) with 95 % confidence intervals (CIs). Statistical significance was set at two-sided $P < 0.05$. We conducted PSM using R revision 4.3.1 (https://www.r-project.org), and the other statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY, USA).

## 3. Results

### 3.1. Characteristics of the population

Fig. 1 shows the flowchart of patient inclusion. Of 1181 patients included in this study, 87 (7.4 %) had LVEF of <60 % within 7 days after stroke onset. After PSM (on confounders of gender, age, diabetes, hypertension, coronary heart disease, atrial fibrillation, smoking, drinking, baseline NIHSS score, systolic blood pressure, fasting plasma glucose, infarction location, and stroke subtype by TOAST), 174 (14.7 %) patients with LVEF of ≥60 % and 87 (7.4 %) patients with LVEF of <60 % were identified. The confounders for PSM were selected according to the results in Supplementary Table 1. We selected variables with statistical significance ($P < 0.05$) in functional outcomes at 90 days.

Before PSM, patients with LVEF of <60 % were older, with a higher NIHSS score, a higher rate of hypertension, atrial fibrillation, and the cardioembolism TOAST subtype (all $P < 0.05$). After PSM, all the differences between the LVEF of <60 % and LVEF of ≥60 % groups were balanced (Table 1).

### 3.2. Comparison of outcomes between patients with LVEF of <60 % and LVEF of ≥60 %

Fig. 2 shows the distribution of the mRS score at 90 days. Compared to the LVEF of ≥60 % group, the LVEF of <60 % group had poor functional outcome at 90 days ($P < 0.001$).

Table 2 shows the pre-PSM multivariate analysis results and post-PSM univariate analysis results for a comparison of functional outcomes between the two groups (LVEF of <60 % and LVEF of ≥60 %). Before PSM, compared to the LVEF of ≥60 % group, the LVEF of <60 % group had 1.85 times the risk of an mRS score of 3–6 at 90 days (32.4 % vs. 59.8 %, OR: 1.85, 95 % CI: 1.01–3.40, $P = 0.048$) and 3.30 times the risk of all-cause mortality at 90 days (2.7 % vs. 14.9 %, OR: 3.30, 95 % CI: 1.53–8.46, $P = 0.003$) after adjusting for gender, age, diabetes, hypertension, coronary heart disease, atrial fibrillation, smoking, drinking, baseline NIHSS score, systolic blood pressure, fasting plasma glucose, infarction location, and stroke subtype by TOAST. However, there was no significant difference between the two groups regarding the mRS score of 2–6 at 90 days, mRS score of 3–6 or 2–6 at discharge, early neurological deterioration, hospital stay of >7 days, and total cost of ≥15,000 RMB (all $P > 0.05$).

**Table 1**
The Baseline Characteristics of Patients with LVEF≥60 % vs LVEF<60 %.

| Variables | Total | Pre-matched Population | | P-value | Post-matched Population | | P-value |
|---|---|---|---|---|---|---|---|
| | | LVEF≥60 % | LVEF<60 % | | LVEF≥60 % | LVEF<60 % | |
| n | 1181 | 1094 | 87 | | 174 | 87 | |
| Gender, n (%) | | | | 0.164 | | | 1.000 |
| Male | 876 (74.2 %) | 806 (73.7 %) | 70 (80.5 %) | | 140 (80.5 %) | 70 (80.5 %) | |
| Female | 305 (25.8 %) | 288 (26.3 %) | 17 (19.5 %) | | 34 (19.5 %) | 17 (19.5 %) | |
| Age, mean (SD), years | 65 (57–71) | 64 (57–71) | 70 (62–77) | <0.001 | 70 (62–77) | 70 (62–76) | 1.000 |
| Diabetes, n (%) | 442 (37.4 %) | 411 (37.6 %) | 31 (35.6 %) | 0.719 | 23 (27.4 %) | 31 (35.6 %) | 0.186 |
| Hypertension, n (%) | 903 (76.5 %) | 845 (77.2 %) | 58 (66.7 %) | 0.025 | 129 (74.1 %) | 58 (66.7 %) | 0.207 |
| Atrial Fibrillation, n (%) | 70 (5.9 %) | 54 (4.9 %) | 16 (18.4 %) | <0.001 | 19 (10.9 %) | 16 (18.4 %) | 0.053 |
| Smoking, n (%) | 634 (53.7 %) | 580 (53.0 %) | 54 (62.1 %) | 0.103 | 85 (48.9 %) | 54 (62.1 %) | 0.059 |
| Drinking, n (%) | 371 (31.4 %) | 343 (31.4 %) | 28 (32.2 %) | 0.872 | 55 (31.6 %) | 28 (32.2 %) | 0.223 |
| Baseline NIHSS score, median (IQR) | 5 (2–8) | 5 (2–12) | 8 (4–12) | 0.001 | 6 (3–10) | 8 (4–12) | 0.623 |
| Systolic Blood Pressure, mean (SD), mmHg | 151 (±24) | 151 (±24) | 150 (±26) | 0.913 | 150 (±23) | 150 (±26) | 0.945 |
| Fasting Plasma Glucose, median (IQR), mmol/L | 5.72 (4.94–7.61) | 5.72 (4.96–7.52) | 5.75 (4.84–8.51) | 0.413 | 5.48 (4.79–7.22) | 5.75 (4.85–8.50) | 0.234 |
| Infarction Location, n (%) | | | | 0.249 | | | |
| Anterior circulation | 862 (73.0 %) | 794 (72.6 %) | 68 (78.2 %) | | 121 (69.5 %) | 68 (78.2 %) | 0.324 |
| Posterior circulation | 276 (23.4 %) | 258 (23.6 %) | 18 (20.7 %) | | 49 (28.2 %) | 18 (20.7 %) | |
| Both | 43 (3.6 %) | 42 (3.8 %) | 1 (1.1 %) | | 4 (2.3 %) | 1 (1.1 %) | |
| Stoke Subtype by TOAST, n (%) | | | | 0.003 | | | 0.240 |
| Large-artery atherosclerosis | 603 (51.1 %) | 556 (50.8 %) | 47 (54.0 %) | | 88 (50.6 %) | 47 (54.0 %) | |
| Cardioembolism | 88 (7.5 %) | 73 (6.7 %) | 15 (17.2 %) | | 19 (10.9 %) | 15 (17.2 %) | |
| Small-artery occlusion | 257 (21.8 %) | 248 (22.7 %) | 9 (10.3 %) | | 33 (19.0 %) | 9 (10.3 %) | |
| Other etiology | 22 (1.9 %) | 21 (1.9 %) | 1 (1.1 %) | | 6 (3.4 %) | 1 (1.1 %) | |
| Undetermined | 211 (17.9 %) | 196 (17.9 %) | 15 (17.2 %) | | 28 (16.1 %) | 15 (17.2 %) | |

LVEF = Left Ventricular Ejection Fraction; NIHSS=National Institutes of Health Stroke Scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

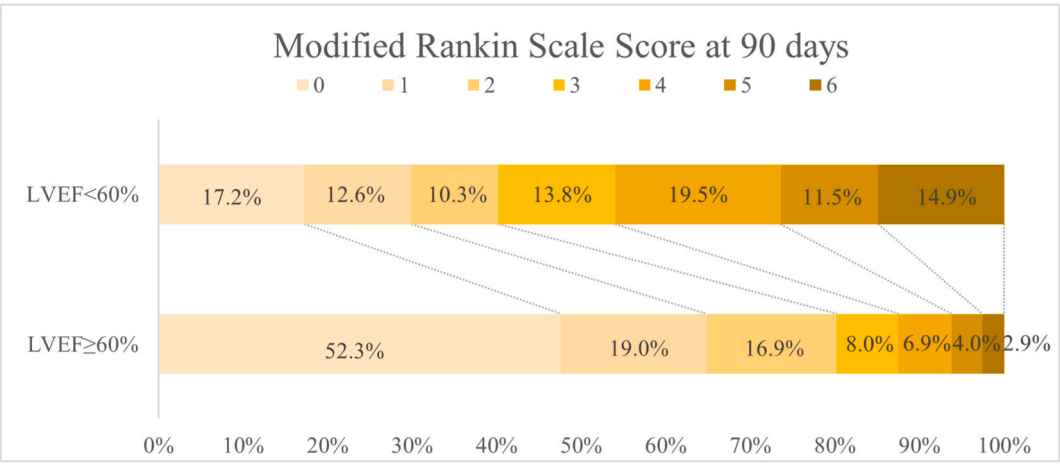


**Fig. 2.** Distribution of scores on the mRS at 90 days. mRS: modified Rankin scale.

**Table 2**
Outcomes of Patients with LVEF≥60 % vs LVEF<60 %.

| Outcomes | Pre-matched Population | | | | Post-matched Population | | | |
|---|---|---|---|---|---|---|---|---|
| | LVEF≥60 % | LVEF<60 % | Multivariate Analysis OR (95%CI)[a] | P-value | LVEF≥60 % | LVEF<60 % | Univariate Analysis OR (95%CI) | P-value |
| n | 1094 | 87 | | | 174 | 87 | | |
| Primary Outcome | | | | | | | | |
| mRS score 3–6 at 90 days | 355 (32.4 %) | 52 (59.8 %) | 1.85 (1.01–3.40) | 0.048 | 38 (21.8 %) | 52 (59.8 %) | 5.32 (3.04–9.30) | <0.001 |
| Secondary Outcomes | | | | | | | | |
| mRS score 2–6 at 90 days | 509 (46.5 %) | 61 (70.1 %) | 1.47 (0.79–2.73) | 0.229 | 50 (28.7 %) | 61 (70.1 %) | 5.82 (3.31–10.23) | <0.001 |
| mRS score 3–6 at Discharge | 484 (44.2 %) | 55 (63.2 %) | 1.13 (0.55–2.32) | 0.737 | 36 (20.7 %) | 55 (63.2 %) | 6.59 (3.73–11.65) | <0.001 |
| mRS score 2–6 at Discharge | 726 (66.4 %) | 73 (83.9 %) | 1.72 (0.72–4.12) | 0.227 | 58 (33.3 %) | 73 (83.9 %) | 10.43 (5.43–20.04) | <0.001 |
| All-cause Mortality at 90 days | 30 (2.7 %) | 13 (14.9 %) | 3.30 (1.53–8.46) | 0.003 | 5 (2.9 %) | 13 (14.9 %) | 5.94 (2.04–17.26) | 0.001 |
| Early Neurological Deterioration | 88 (8.0 %) | 5 (5.7 %) | 0.60 (0.23–1.59) | 0.307 | 10 (5.7 %) | 5 (5.7 %) | 1.00 (0.33–3.02) | 1.000 |
| Hospital Stays >7 days | 641 (58.6 %) | 61 (70.1 %) | 1.12 (0.66–1.89) | 0.673 | 87 (50.0 %) | 61 (70.1 %) | 2.35 (1.36–4.05) | 0.002 |
| Total Cost≥15000 RMB | 462 (42.2 %) | 49 (56.3 %) | 1.01 (0.59–1.72) | 0.972 | 58 (33.3 %) | 49 (56.3 %) | 2.58 (1.52–4.37) | <0.001 |

LVEF = Left Ventricular Ejection Fraction; mRS = modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

[a] Adjusted by gender, age, diabetes, hypertension, coronary heart disease, atrial fibrillation, smoking, drinking, baseline NIHSS score, systolic blood pressure, fasting plasma glucose, and stoke subtype by TOAST.

After PSM, the differences in all the poor outcomes except early neurological deterioration were statistically significant between the two groups. Compared to the LVEF of ≥60 % group, the LVEF of <60 % group had 5.32 times the risk of an mRS score of 3–6 at 90 days (21.8 % vs. 59.8 %, OR: 5.32, 95 % CI: 3.04–9.30, $P < 0.001$), 5.82 times the risk of an mRS score of 2–6 at 90 days (28.7 % vs. 70.1 %, OR: 5.82, 95 % CI: 3.31–10.23, $P < 0.001$), 6.59 times the risk of an mRS score of 3–6 at discharge (20.7 % vs. 62.3 %, OR: 6.59, 95 % CI: 3.73–11.65, $P < 0.001$), 10.43 times the risk of an mRS score of 2–6 at discharge (33.3 % vs. 83.9 %, OR: 10.43, 95 % CI: 5.43–20.04, $P < 0.001$), 5.94 times the risk of all-cause mortality at 90 days (2.9 % vs. 14.9 %, OR: 5.94, 95 % CI: 2.04–17.26, $P = 0.001$), 2.35 times the risk of hospital stay of >7 days (50.0 % vs. 70.1 %, OR: 2.35, 95 % CI: 1.36–4.05, $P = 0.002$), and 2.58 times the risk of total cost of ≥15,000 RMB (33.3 % vs. 56.3 %, OR: 2.58, 95 % CI: 1.52–4.37, $P < 0.001$).

### 3.3. Subgroup analysis

We included 1093 patients with non-cardioembolic stroke and 88 patients with cardioembolic stroke. In the 1093 patients with non-cardioembolic stroke, we identified 72 (6.6 %) patients with LVEF of <60 % and 1021 (93.4 %) patients with LVEF of ≥60 % (Table 3). The differences in all functional outcomes (mRS score of 3–6 at 90 days, mRS score of 2–6 at 90 days, mRS score of 3–6 at

**Table 3**
Subgroup analysis in patients with non-cardioembolic stroke and patients with cardioembolic stroke.

| Outcomes | Patients with Non-cardioembolic Stroke | | | | Patients with Cardioembolic Stroke | | | |
|---|---|---|---|---|---|---|---|---|
| | LVEF≥60 % | LVEF<60 % | Multivariate Analysis OR (95%CI)[a] | P-value | LVEF≥60 % | LVEF <60 % | Multivariate Analysis OR (95%CI)[a] | P-value |
| n | 1021 | 72 | | | 73 | 15 | | |
| Primary Outcome | | | | | | | | |
| mRS score 3–6 at 90 days | 318 (31.1 %) | 45 (62.5 %) | 3.04 (1.76–5.26) | <0.001 | 37 (50.7 %) | 8 (46.7 %) | 1.15 (0.21–6.26) | 0.872 |
| P for interaction | 0.982 | | | | | | | |
| Secondary Outcomes | | | | | | | | |
| mRS score 2–6 at 90 days | 468 (45.8 %) | 51 (70.8 %) | 2.41 (1.37–4.24) | 0.002 | 41 (56.2 %) | 10 (66.7 %) | 1.58 (0.30–8.42) | 0.595 |
| P for interaction | 0.310 | | | | | | | |
| mRS score 3–6 at Discharge | 444 (43.5 %) | 48 (66.7 %) | 2.23 (1.30–3.81) | 0.003 | 40 (54.8 %) | 7 (46.7 %) | 0.88 (0.17–4.51) | 0.878 |
| P for interaction | 0.837 | | | | | | | |
| mRS score 2–6 at Discharge | 678 (66.4 %) | 63 (87.5 %) | 3.21 (1.54–6.71) | 0.002 | 48 (65.8 %) | 10 (66.7 %) | 1.36 (0.22–8.36) | 0.739 |
| P for interaction | 0.935 | | | | | | | |
| All-cause Mortality at 90 days | 24 (2.4 %) | 11 (15.3 %) | 6.40 (2.75–14.89) | <0.001 | 6 (8.2 %) | 2 (13.3 %) | 0.96 (0.09–10.81) | 0.975 |
| P for interaction | 0.945 | | | | | | | |
| Early Neurological Deterioration | 83 (8.1 %) | 4 (5.6 %) | 0.57 (0.19–1.67) | 0.303 | 5 (6.8 %) | 1 (6.7 %) | 0.89 (0.03–27.04) | 0.949 |
| P for interaction | 0.815 | | | | | | | |
| Hospital Stays >7 days | 549 (58.2 %) | 50 (69.4 %) | 1.44 (0.83–2.50) | 0.190 | 47 (64.4 %) | 11 (73.3 %) | 2.44 (0.38–15.70) | 0.349 |
| P for interaction | 0.486 | | | | | | | |
| Total Cost≥15000 RMB | 421 (41.2 %) | 41 (56.9 %) | 1.65 (0.97–2.80) | 0.066 | 41 (56.2 %) | 8 (53.3 %) | 0.49 (0.08–2.99) | 0.437 |
| P for interaction | 0.875 | | | | | | | |

LVEF = Left Ventricular Ejection Fraction; mRS = modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale.
[a] Adjusted by gender, age, diabetes, hypertension, coronary heart disease, atrial fibrillation, smoking, drinking, baseline NIHSS score, systolic blood pressure, fasting plasma glucose, and stoke subtype by TOAST.

discharge, mRS score of 2–6 at discharge; $P < 0.001$, $P = 0.002$, $P = 0.003$, $P = 0.002$, respectively) and all-cause mortality at 90 days ($P < 0.001$) between the LVEF of ≥60 % and LVEF of <60 % groups were statistically significant. However, the differences in early neurological deterioration ($P = 0.303$), hospital stay of >7 days ($P = 0.190$), and total cost of ≥15,000 RMB ($P = 0.066$) between the two groups were not statistically significant.

In the 88 patients with cardioembolic stroke, we identified 15 (17.0 %) patients with LVEF of <60 % and 73 (83.0 %) patients with LVEF of ≥60 % (Table 3). The differences between the LVEF of ≥60 % and LVEF of <60 % groups regarding an mRS score of 3–6 at 90 days ($P = 0.872$), an mRS score of 2–6 at 90 days ($P = 0.595$), an mRS score of 3–6 at discharge ($P = 0.878$), an mRS score of 2–6 at discharge ($P = 0.939$), all-cause mortality at 90 days ($P = 0.975$), early neurological deterioration ($P = 0.949$), hospital stay of >7 days ($P = 0.349$), and total cost of ≥15,000 RMB ($P = 0.437$) were all not statistically significant.

However, there were no significant interactions between LVEF and cardioembolism for all outcomes (all P for interaction >0.05). Thus, the results of subgroup analyses were consistent with the main analysis in Table 2.

### *3.4. LVEF grouped by 55 % or 50 %*

When tested as a continuous variable, the LVEF was associated with all functional outcomes, whether at discharge or at 90 days, except early neurological deterioration, hospital stay of >7 days, and total cost of ≥15,000 RMB. When grouped by 55 % or 50 %, the LVEF was still significantly associated with an mRS score of 3–6 at 90 days but was not always significantly associated with other functional outcomes (see Supplementary Table 2).

## 4. Discussion

In this prospective cohort study of patients with AIS, LVEF of <60 % was associated with short-term functional disability. This finding is consistent with previous research [16,17]. In the Acute Stroke Registry and Analysis of Lausanne study, LVEF≤35 % during hospitalization was associated with a composite outcome of an mRS score of 3–6 plus mortality at 1 week (19.5 % vs. 7.8 %) and 12 months (36.1 % vs. 16.5 %) in patients with AIS [16]. In patients with large-vessel occlusion, LVEF of <50 % assessed within 6 months after AIS was associated with poor functional outcomes (defined as an mRS score of 3–6) after endovascular thrombectomy (68.0 % vs. 51.9 %) [10]. In a retrospective study of patients with AIS, LVEF of <55 % during hospitalization was associated with poor functional outcomes (defined as an mRS score of 3–6) at discharge (54.7 % vs. 42.7 %) and 90 days (54.1 % vs. 30.6 %) [17]. However, this is the

first study to demonstrate that LVEF of <60 % is able to increase the risk of poor functional outcomes (defined as an mRS score of 3–6) at 90 days compared to LVEF of ≥60 % (59.8 % vs. 32.4 %).

Sufficient cerebral perfusion plays an important role in the early recovery of neurological function and the prevention of neurological deterioration in patients with AIS [18]. Cerebral perfusion depends on cerebral autoregulation and cardiac output. However, cerebral autoregulation is impaired in the ischemic area after a stroke shock [19], and cardiac output becomes the main factor influencing cerebral perfusion [20]. Thus, a low cardiac output assessed using the LVEF might affect adverse outcomes in patients with AIS. In a heterogeneous clinical cohort, LVEF values from 60 % to 65 % were found to be associated with higher survival [14]. However, no study has reported the best value range of the LVEF for functional outcomes in patients with AIS.

As reported before, patients of cardioembolic stroke tend to be severe and have lower LVEF [6,9,10]. A better LVEF might improve their functional outcome. However, we failed to demonstrate the association between LVEF and functional outcomes in patients with cardioembolic stroke because of a small number of cardioembolic stroke in this study. The analysis in patients of non-cardioembolic stroke showed that LVEF of <60 % was associated with functional disability. Whether they have cardioembolic stroke or not, patients are vulnerable to left ventricular systolic dysfunction in the acute phase because of the autonomic stress response to stroke [18]. Mechanisms underlying sympathetic hyperactivity [21], the hypothalamic–pituitary–adrenal axis [22], and immune–inflammatory responses [23] have been proposed to explain this phenomenon [3,18,24]. In this study, we speculated that AIS impairs the LVEF and that this impaired LVEF increases the risk of poor functional outcomes. A bidirectional interaction exists between the brain and the heart [18,25]. In experimental animal models, β-blockade with metoprolol was effective in preventing the development of cardiac dysfunction after middle cerebral artery occlusion [26]. However, no clinical study has proven that the use of β-blockers can improve functional outcomes by reducing cardiac function damage.

### *4.1. Limitations*

This study has a few limitations. First, we only included patients who underwent echocardiography within 7 days after stroke onset. This resulted in the exclusion of patients with large cerebral infarction or severe posterior circulation infarction, as they could not complete echocardiography because of being in intensive care. As reported before, the more severe the stroke is, the more likely cardiac dysfunction will occur in the acute phase [6]. In addition, nearly 50 % of patients were excluded, which resulted in a different distribution of stroke subtypes compared to nationwide studies [27]. Selection bias may also affect the main results. Second, compared to previous studies (LVEF <55 %, 137 of 1554 patients) [17], patients with LVEF of <60 % identified in our study (87 of the whole population of 1181, 88 of 1093 patients after excluding those with cardioembolic stroke) were relatively fewer. The multivariate analyses in the pre-PSM population were not statistically significant in some secondary outcomes, perhaps because of the unequal distribution of patients between groups. Third, the LVEF was not the best index for evaluating cardiac function with a larger deviation and a smaller variation.

### *4.2. Strengths*

This study also has some strengths. First is the prospective design of the study. Second, we included patients with the LVEF assessed in the acute phase. Third, subgroup analysis in patients with non-cardioembolic stroke.

## 5. Conclusions

This study found that the clinically assessed LVEF is associated with functional outcomes in patients with AIS. In the acute phase, LVEF of <60 % predicts poor functional outcomes. Our results suggest that therapeutic strategies for improving cardiac function might in turn help improve functional outcomes in patients with AIS.

## Ethics approval and consent to participate

The SPARK study was conducted in accordance to the Declaration of Helsinki, and had been approved by the Institutional Review Board of Tianjin Huanhu Hospital at December 16th, 2022. The number of the approval was 2022-158.The informed consents were obtained from all participants or their legal guardians.

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## Availability of data and materials

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

## CRediT authorship contribution statement

**Guojuan Chen:** Writing – review & editing, Writing – original draft, Software, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Peng Ding:** Writing – review & editing, Resources, Investigation, Data curation. **Liqin Yang:** Resources, Investigation. **Xueqing Liu:** Software, Resources, Investigation. **Delin Yu:** Resources, Project administration, Methodology. **Wei Yue:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29352.

## List of Abbreviations

| | |
|---|---|
| AIS | acute ischemic stroke |
| LVEF - | left ventricular ejection fraction |
| mRS | modified Rankin Scale |
| NIHSS | National Institutes of Health Stroke Scale |
| TOAST | Trial of ORG 10172 in Acute Stroke Treatment |
| PSM | propensity score matching |
| OR | odds ratio |
| CI | confidence interval |

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